REMARKS/ARGUMENTS

Applicants acknowledge with appreciation the withdrawal of the previous rejections of claims under 35 U.S.C. §112, first paragraph (Office Action, page 2, #3).

Applicants respectfully note again that the Attorney Docket Number for this application has been changed from 20164000US5 to ARG010RC; correction of the Attorney Docket Number for this application is respectfully requested.

Claims 89, 91, 92, 94, 95, 99, 101, 103-113, 115-121, and 140-144 were pending in the application. Claims 89, 91, 92, 94, 95, 103, 115, 117, 118, 119, 121, 140, and 141 have been canceled without prejudice in order to expedite prosecution of the remaining claims. Applicants expressly reserve the right to prosecute these claims in a continuing application.

The Claim of Priority to Earlier Applications Should Be Accepted

The Office Action (dated February 6, 2008, page 2, #4) concludes that the benefit of priority to earlier applications is denied because "the applications do not disclose the invention of the instant claims." Applicants respectfully disagree with this conclusion, as support for the present claims is found in the '612 priority application, as further discussed in detail below. Applicants note that in order to clearly address the concerns in the Office Action, the discussion in this response focuses on the first-filed '612 priority application, but the other applications in the priority chain also provide support for the claims as set forth herein for the '612 application.

The Office Action states that "the method step employed in instant Claim 101 comprising "treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors" is not found in the '612 application. Applicants respectfully disagree. Applicants respectfully note that the '612 application states that "[a]ccording to the method of the invention, the **tissue source may be treated prior to culturing to enrich the proportion of dendritic precursor cells** relative to other cell types" (see page 13, lines 16-18; this tissue source is described earlier on page 13 (lines 4-8) as "a tissue source comprising dendritic cell precursors....") This same statement is found in the '357 application on page 15, lines 16-18. Accordingly, Applicants respectfully submit that support for this method step is found in these

priority applications and that the benefit of priority to these applications and their filing dates should be given full effect.

The Office Action further states that "neither the '612 nor the '357 applications disclose the cells being cultured with an antigen as is recited in the last step of Claims 101 and 120." Applicants respectfully disagree. The last step of claims 101 and 120 specify "wherein the dendritic cells are cultured *in vitro* in the presence of an antigen for a time sufficient to allow the antigen to be fragmented and presented." Applicants respectfully note that the '612 application describes this step on page 22, lines 10-20, which state:

> The antigen-activated dendritic cells of the invention are produced by exposing antigen, *in vitro*, to the dendritic cells prepared according to the method of the invention. Dendritic cells are plated in culture dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells."

Antigen fragmentation is discussed, for example, in the immediately preceding paragraph (page 21, line 30, through page 22, line 10) which states:

> "Foreign and autoantigens are processed by the dendritic cells of the invention to retain their immunogenic form. The immunogenic form of the antigen implies retaining the native epitopes of immunogenic determinants on the antigen while processing the antigen through fragmentation to produce a form of the antigen that can be recognized by and stimulate T cells. * * *

Support for the last step of claims 101 and 120 is also found in the '612 application in Examples 2 and 3 on page 40. Example 2 is entitled, "Antigen activated dendritic cells as immunogens" and states (page 40, line 5) that

> "[d]endritic cells prepared according to the method described in Example 1 are plated.... The cells are incubated in RPMI 1640 containing...GM-CSF.... Antigen is added to the dendritic cell cultures and the cultures are incubated with antigen for approximately 4 hours or for sufficient time to allow the dendritic cells to handle the antigen in an immunologically relevant form, or in a form that can be recognized by T cells. Such handling of the antigen by the dendritic cells involves the dendritic cells 1) acquiring, 2) processing, and 3) presenting the antigen to the T cells in a form which is recognized by the T cells. Following binding of the antigen to the dendritic cells the cells are collected from the culture...."

Similarly, Example 3 (page 40, lines 22-26) states that "[d]endritic cells prepared as described in Example 1 are pulsed with a protein antigen for a time sufficient to allow the dendritic cells to acquire, process and present the modified antigen on the surface of the dendritic cells."

The same language cited above from the '612 application is also found in the '357 application on page 27, lines 3-18, in Example 3 on page 56, and in Example 4 on page 57. In view of this discussion in the '612 and '357 priority applications, Applicants respectfully submit that these applications do support the last step of claims 101 and 120 and that the priority claim to these applications should be given full weight.

"Finally," the Office Action states (page 2, #4), neither [priority] application discloses a microorganism antigen, in particular a BCG antigen" and concludes that "[a]ccordingly, the benefit of priority to said applications is denied." Applicants respectfully disagree with this rationale and conclusion because the claims as originally filed (and pending claims 101 and 120) do not require the use of a particular antigen. Indeed, as discussed in the Background Section of the application, it was already well-known in the art that dendritic cells present antigens to T cells: "Dendritic cells bind and modify antigens in a manner such that that modified antigen when presented on the surface of the dendritic cell can activate T-cells to participate in the eventual production of antibodies" (see '612 application at page 6, lines 8-11); further, "[t]he efficacy of dendritic cells in delivering antigens in such a way that a strong immune response ensues... is widely acknowledged, **but the use of these cells is hampered by the fact that there are very few** in any given organ" ('612 application at page 2, lines 16-20). Thus, the '612 application focused instead on improved methods of producing compositions of dendritic cells "in sufficient quantities to be used to treat or immunize animals or humans with dendritic cells which have been activated with antigens," which "[t]he present invention provides for the first time" (specification at page 40, lines 25-28 and page 9, line 35 through page 10, line 4). The '612 application also focused on the improved antigen-activated dendritic cells taught in the application, which are "**much more potent in presenting antigens to primed T cells than corresponding cultures of mature dendritic cells**...." (see, *e.g.*, present specification at page 37, lines 17-20). For these reasons, the claims originally filed with the '612 application and the

currently pending claims 101 and 120 specified that the cells were pulsed with "an antigen," (see, *e.g.*, '612 original claim 36), rather than with a particular antigen.

Accordingly, Applicants respectfully submit that whether the priority applications mention mycobacterial antigens or a BCG antigen is not germane to whether claims 101 or 120, for example, are entitled to the priority claim to earlier applications because these claims do not specify either a mycobacterial antigen or a BCG antigen. Applicants note that in order to advance prosecution, a number of claims have been canceled, including claims 94 and 95 which specified a mycobacterium and a mycobacterium which is BCG, respectively. Applicants also respectfully note that since the Restriction Requirement of March 12, 2002, there have been extensive amendments to the claims and extensive discussion of the invention which are believed to have clarified the scope of the claims and so rendered this Restriction Requirement moot. Accordingly, Applicants respectfully request that the Restriction Requirement of March 12, 2002, be withdrawn; alternatively, Applicants respectfully request consideration and examination of the claims (particularly claims 101 and 120) as linking claims so that prosecution may be advanced.

Further, Applicants respectfully submit that each of the now-pending claims is fully supported by the '612 specification. The discussion of support for pending claims below is grouped by dependency for ease of review.

Support for independent claim 101 can be found, for example, in the '612 application on page 8, lines 15-19 ("Another embodiment of the invention [is] **antigen-activated dendritic cells prepared according to the method of the invention** [in] which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells") and on page 10, lines 2-5 ("**Another object of this invention is to provide novel immunogens comprising the dendritic cells of this invention which have been exposed to antigen and express modified antigen on their surface**"). The '612 application continues: "The **antigen-activated dendritic cells of the invention are produced by exposing antigen, *in vitro*, to the dendritic cells prepared according to the method of the invention**. Dendritic cells are plated in culture dishes and exposed to antigen in a sufficient amount and for

a sufficient period of time to allow the antigen to bind to the dendritic cells" (page 22, lines 10-20).

The method limitations of claim 101 are also supported in the '612 priority application, for example, on page 2, lines 7-9, which state that "a method is provided for culturing proliferating dendritic cell precursors and for their maturation *in vitro* to mature dendritic cells." Support can also be found in the '612 priority application in original dependent claim 36 and original independent claim 17 and, which were as follows:

> 36. A **composition comprising antigen-activated dendritic cells wherein dendritic cells prepared according to claim 17 are pulsed with an antigen** and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.
>
> 17. A method of producing a population of mature dendritic cells from proliferating cell cultures comprising:
> a) providing a tissue source comprising dendritic cell precursors;
> b) treating the tissue source to obtain a population of cells suitable for culture *in vitro*;
> c) culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain nonadherent cells and cell clusters;
> d) subculturing the nonadherent cells and cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors;
> e) serially subculturing the cell aggregates one or more time to enrich the proportion of dendritic cell precursors; and
> f) continuing to culture the dendritic cell precursors for a period of time sufficient to allow them to mature into mature dendritic cells.

A comparison of these original claims of the '612 application to claim 101 shows that the limitations are essentially the same; accordingly, Applicants respectfully submit that claim 101 is fully supported by the '612 priority application.

Similarly, presently pending claim 120 specifies "[a]n *in vitro* composition comprising mature dendritic cells derived from an *in vitro* culture of a population of enriched and expanded proliferating precursor cells, wherein said dendritic cells are contacted *in vitro* with antigen in the presence of GM-CSF for a sufficient time for antigen fragmentation and presentation to occur." Support for claim 120 can be found, for example, in the priority Application No.

07/861,612 on page 8, lines 15-19: "Another embodiment of the invention [is] antigen-activated dendritic cells prepared according to the method of the invention [in] which antigen-activated **dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells.**" The '612 application continues on page 22, lines 10-20: "The **antigen-activated dendritic cells of the invention are produced by exposing antigen, *in vitro*, to the dendritic cells prepared according to the method of the invention.** Dendritic cells are plated in culture dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells." The importance of culture in GM-CSF is discussed throughout the '612 application, particularly, for example, on page 16, lines 2-6, which state that "GM-CSF has surprisingly been found to promote the proliferation in vitro of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors." In view of these teachings of the '612 application, Applicants respectfully submit that the present claims are fully supported by the '612 priority application and meet the requirements of 35 U.S.C. § 112.

Claim 104 specifies "[t]he composition according to claim 101, wherein the tissue source is blood." Support can be found in the '612 application, for example, on page 14, lines 5-19, which begin: "When blood is used as a tissue source...."

Claim 107 specifies "[t]he composition according to claim 104, wherein the concentration of GM-CSF in the culture medium is about 30-100 U/ml. Support can be found in the '612 application, for example, on page 14, lines 10-12, which state that "...cells from blood are cultured in the presence of GM-CSF at a concentration of between about 30 and 100 U/ml."

Claim 112 specifies "[t]he composition according to claim 104, wherein the tissue source is treated to remove red blood cells." Support can be found in the '612 application, for example, on page 14, lines 7-19, which begin "[a]ccording to the preferred method of the invention...." (line 7) and continue, "[c]ells are pelleted and washed by centrifugation.... Platelets and red blood cells are depleted by suspending the cell pellet in a mixture of medium and ammonium chloride" (lines 10-13).

Claim 105 specifies "[t]he composition according to claim 101, wherein the tissue source is bone marrow." Support can be found in the '612 application, for example, on page 13, lines 29-30, which state: "When bone marrow is used as the tissue source...."

Claim 108 has been amended and specifies "[t]he composition according to claim 105, wherein the concentration of GM-CSF in the culture medium is about 500-1000 U/ml." Support can be found in the '612 application, for example, on page 16, lines 18-20, which state: "Doses between about 500-1000 U/ml are preferred for cultures of cells obtained from marrow."

Claim 113 specifies "[t]he composition according to claim 105, wherein the tissue source is treated to remove B cells and granulocytes." Support can be found in the '612 application, for example, on page 13, line 29 through page 14, line 4: "When bone marrow is used as the tissue source, it is preferred to remove B cells.... In addition, it is preferred to use procedures which minimize the number of granulocytes...."

Claim 106 specifies "[t]he composition according to claim 101, wherein GM-CSF is present in the culture medium at a concentration of about 1-1000 U/ml." Support can be found in the '612 application, for example, on page 16, lines 9-10: "Preferably, the cells are cultured in the presence of between about 1 and 1000 U/ml of GM-CSF."

Claim 109 specifies "[t]he composition according to claim 101, wherein the cell aggregates are blood derived and are subcultured from about one to five times." Support can be found in the '612 application, for example, on page 14, lines 5-19, beginning "[w]hen blood is used as a tissue source..." and on page 18, line 26 through page 19, line 10, beginning "[t]o further expand the population of dendritic cell, cell aggregates may be serially subcultured multiple times..." (page 18, lines 26-27) and ending, "[p]referably, cells can be serially subcultured...between about one to five times" (page 19, lines 8-10).

Claim 110 specifies "[t]he composition according to claim 101, wherein the cell aggregates are subcultured one to five times." Support can be found in the '612 application, for example, on page 18, line 26 through page 19, line 10, beginning "[t]o further expand the population of dendritic cell, cell aggregates may be serially subcultured multiple times..." (page 18, lines 26-27) and ending, "[p]referably, cells can be serially subcultured...between about one to five times" (page 19, lines 8-10).

Claim 111 specifies "[t]he composition according to claim 101, wherein the culture medium is selected from the group consisting of RPMI 1640, DMEM and α-MEM, and wherein the culture medium is supplemented with serum." Support can be found in the '612 application, for example, on page 15, lines 18-21, "[p]referred medias include RPMI 1640, DMEM and α-MEM, with added amino acids and vitamins supplemented with an appropriate amount of serum...."

Claim 116 specifies "[a] pharmaceutical composition comprising a therapeutically effective amount of the composition according to claim 101." Support can be found in the '612 application, for example, on page 24, lines 4-11, which state that "[t]he activated dendritic cells...may be formulated for use as vaccines or pharmaceutical compositions with suitable carriers...."

Claim 99 specifies "[t]he pharmaceutical composition according to claim 116, wherein the dendritic cells express an amount of the fragmented antigen to provide between about 1 to 100 micrograms of the fragmented antigen in said pharmaceutical composition." Support can be found in the '612 application, for example, on page 24, lines 7-13, "[t]he vaccines or pharmaceutical compositions comprising the modified antigens or the antigen-activated dendritic cells of the invention would be administered in therapeutically effective amounts sufficient to elicit an immune response. Preferably, between about 1 to 100 micrograms of modified antigen, or its equivalent when bound to dendritic cells, should be administered per dose."

Claim 142 specifies "[t]he composition according to claim 101, wherein the dendritic cell precursors are human." Support can be found in the '612 application, for example, on page 15, lines 13-26, beginning "[t]he growth medium for the cells at each step of the method of the invention should allow for the survival and proliferation of the precursor dendritic cells" (lines 13-15) and ending, "[c]ells from human tissue may also be cultured in medium supplemented with human serum...." (lines 24-26).

Claim 143 specifies "[t]he composition of dendritic cell precursors according to claim 142, wherein the dendritic cell precursors are obtained from blood." Support can be found in the '612 application, for example, on page 14, lines 5-19, beginning "[w]hen blood is used as a tissue source...."

Claim 144 specifies "[t]he composition of dendritic cell precursors according to claim 142, wherein the dendritic cell precursors are obtained from bone marrow." Support can be found in the '612 application, for example, on page 13, lines 29-30, beginning "when bone marrow is used as the tissue source...."

In view of the above discussion and information, Applicants respectfully submit that the pending claims are entitled to the priority date of the '612 application.

The Rejections of Claims under 35 U.S.C. § 102 Should Be Withdrawn

The Office Action (page 2, #6) has maintained the rejection of claims 89, 91, 92, 94, 95, 99, 101, 103-113, 115-121, and 140-144 under 35 U.S.C. § 102(a) over Pancholi *et al.* (1992) *Immunology* 76: 217-224. The Office Action indicates (page 2, #4 and page 3, third full paragraph) that the claims are not entitled to the priority date of App. No. 07,861,612 ("the '612 application") and that therefore the Pancholi reference is available as prior art, even though it was published after the priority date of the '612 application. Applicants respectfully disagree with this assessment and traverse this rejection.

Applicants note that claims 89, 91, 92, 94, 95, 103, 115, 117, 118, 119, 121, 140, and 141 have been cancelled, and that claim 108 has been amended to clarify the scope of the invention and in order to expedite prosecution. Support for each pending claim in the '612 priority application is discussed in detail above. In view of this support for the pending claims in the '612 application, Applicants respectfully submit that the claims are entitled to the '612 priority date (*i.e.*, April 1, 1992) and that Pancholi therefore is not available as prior art against the claims. Accordingly, Applicants request that this rejection of claims be reconsidered and withdrawn.

However, Applicants also note that even if the Pancholi reference were available as art against the application, it would not anticipate the cells of the present claims because Applicants' cells are different from the cells taught by the Pancholi reference. Particularly, as discussed previously in this case (*e.g.*, in the Response filed 10 March 2006, page 11, third paragraph) and as required by the claims, the **cells of the present invention are cultured in GM-CSF**, which

promotes the proliferation *in vitro* of precursor dendritic cells (see, *e.g.*, '612 application on page 16, lines 2-6, stating that "**GM-CSF has surprisingly been found to promote the proliferation *in vitro* of precursor dendritic cells**"; and on page 16, lines 23-24, stating that "[i]n the absence of GM-CSF, no colonies develop"). Culture of the cells in **GM-CSF provides the enriched and expanded population of proliferating dendritic cell precursors required** by the present claims.

In contrast, the Pancholi reference focuses on the production of mycobacterial-reactive T cells. The dendritic cells discussed in the Pancholi reference are isolated directly from blood (see Abstract, discussing "[d]endritic cells from blood...." and also the Materials and Methods section on page 218, which describes the "purification of dendritic cells" from blood (see page 218, left column, last paragraph, section entitled "Preparation of APC"; and section entitled "Further purification of dendritic cells...." on page 218, right column, first full section)). The cells described in the Pancholi reference were **not** cultured in GM-CSF. In some instances, sorted dendritic cells were assessed for their ability to induce T cells to proliferate; the Pancholi reference concludes (paragraph bridging pages 220-221) that "sorted dendritic cells were ***several times*** better than sorted monocytes in stimulating bulk T cells...."

In contrast to Pancholi's blood-derived dendritic cells, cells prepared according to the present invention are much better at stimulating T cells. As demonstrated in the '612 application in Figure 7 and described in Example 1 on pages 33-34, "MLR-stimulating activity was monitored in the GM-CSF treated blood cultures" (see '612 application at page 33, line 25-26). "After 3 weeks [of culture in GM-CSF], typical mature dendritic cells had become abundant, and these indeed stimulated comparably to their splenic counterparts...." (see '612 application at page 34, lines 16-18). "We conclude that the aggregates of proliferating dendritic cells have some MLR stimulating activity but that it is the mature released cells that are fully potent, some ***100-300 times more active on a per cell basis than the populations in the starting culture*** at 1-7 days" (see '612 application at page 34, lines 21-15).

Thus, cells prepared according to the present invention are much more active in stimulating T cell proliferation in an MLR when compared to a control population ("some 100-300 times more active") than the cells taught by the Pancholi reference ("several times"). In view of this superior ability of the cells of the present invention to stimulate T-cells, Applicants

respectfully submit that the cells of the present claims are different from the cells of Pancholi and so the Pancholi reference, even if it were available as prior art against the claims, would not anticipate the claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of the claims.

The Office Action (page 3, #9) has also rejected claims 101, 103-113, 115, 116, 118-121, 140, and 151 under 35 U.S.C. §102(b) over Steinman *et al.* (1974) as evidenced by O'Doherty (1994). The Office Action states (page 4, first full paragraph) that "Steinman et al. teaches an in vitro composition comprising a mature DC...." and concludes that "[t]he reference clearly anticipates the claimed invention." Applicants respectfully disagree with this conclusion and traverse this rejection.

The Steinman reference, like the Pancholi reference, does not teach culture of dendritic cell precursors in the presence of GM-CSF. In contrast, the cells of the present invention are cultured in GM-CSF, which promotes the proliferation *in vitro* of precursor dendritic cells (see, *e.g.*, '612 application on page 16, lines 2-6, stating that "GM-CSF has surprisingly been found to promote the proliferation *in vitro* of precursor dendritic cells"; and on page 16, lines 23-24, stating that "[i]n the absence of GM-CSF, no colonies develop"). Culture of the cells in **GM-CSF provides the enriched and expanded population of proliferating dendritic cell precursors required by the present claims, and mature dendritic cells produced from these precursors are different** from previously reported cells. For example, as discussed above, cells of the present invention are much more active in stimulating T cell proliferation in an MLR when compared to a control population ("some 100-300 times more active") than previously reported cells such as, for example, those taught by the Pancholi reference. The cited Steinman reference does not teach the culture of dendritic cell precursors in the presence of GM-CSF and so these cells would lack the superior properties of the cells of the present invention. Further, the Steinman reference does not teach the preparation of antigen-activated dendritic cells as taught in the present specification and as presently claimed; thus, it does not appear that the Steinman reference teaches all the elements of the claims. Accordingly, Applicants respectfully submit that the Steinman reference does not anticipate the present claims, and respectfully request reconsideration and withdrawal of this rejection.

Applicants respectfully note that when product-by-process claims are examined, "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product" (MPEP § 2113). Here, Applicants have described the unexpected superiority of the cells of the invention in stimulating T cells in an MLR (as particularly discussed above in view of the Pancholi reference). Applicants have also discussed the advantage of the invention of providing dendritic cells in sufficient quantities *in vitro* for clinical treatment (see, *e.g.*, the Background section of the '612 application on page 3, line 19 through page 4, line 17), and previously discussed that dendritic cells prepared according to the claimed methods are more effective at presenting antigen to T cells *in vitro* than previously known cells (for example, in comparison to the cells taught by the Pancholi reference, as discussed in the previous response filed on April 10, 2007, on pages 10-11). Applicants respectfully disagree with the conclusion in the Office Action that "no meaningful comparison can be made" with the cells taught by the Pancholi reference, as the comparison of stimulatory ability in an MLR is often used in the art for evaluating differences among antigen-presenting cells. Applicants respectfully submit that all of these differences are unexpected differences over the prior art which should be accepted as demonstrating patentability of the claimed invention.

Applicants note in this regard that previous Office Actions in this case have acknowledged that the cells of the present invention differ from previously-described cells due to the effects of GM-CSF on the cells. Particularly, for example, a rejection of claims was previously made over a combination of references that included a reference similar to the Pancholi reference: Inaba *et al.* (1990) *J. Exp. Med.* 172: 631-640, "the Inaba reference" (see Office Action of 2 July 2002). Particularly, the Office Action (of 2 July 2002, page 6, #14) stated that:

> Inaba et al. teaches dendritic cells pulsed with polypeptide or peptide antigens...that process and present antigen...."

However, the Inaba reference taught dendritic cells which were prepared without culturing in GM-CSF. The Inaba reference was discussed in several subsequent papers, and Applicants ultimately distinguished the Inaba reference in the Amendment filed 2 June 2004 (page 7, part I) by noting that :

> The so-called 'dendritic cells' of Inaba cannot be pulsed with native protein antigen after a *single day* in culture .... Inaba later states that his 'dendritic cells' can 'only capture antigens for a short period.' (page 198, paragraph spanning pp. 198-199). Thus, the so-called 'dendritic cells' of Inaba can uptake native protein antigens for only a short time, and lose this ability after a mere day in culture.
>
> In contrast, the Application describes the uptake of native protein antigen by dendritic cells *several days* after the cells are cultured. For example, in Fig. 13, the Application provides results showing that dendritic cells which were cultured for 6 days in GM-CSF, then exposed for 2 hours to GCG antigen, and then cultured another 2 days in GM-CSF were still able to express antigen from the native BCG antigen that they had been pulsed with. In other words, before the cells' initial exposure to BCG antigen, the cells had been cultured for *six days*, and were still able to uptake, process, and present BCG antigen.
>
> Thus, the cells of Inaba are not the result of the same process as Applicants' claimed cells, nor are the cells of Inaba the same cells as Applicants' cells.
>
> Moreover, because the cells of Inaba are not able to be cultured for more than a single day, the ordinarily skilled artisan would realize that Inaba's so-called 'dendritic cells' cannot be enriched and expanded, as is required by the presently claimed composition. Culturing the cells of Inaba for longer than one day will cause them to lose their ability to uptake native protein antigen. Thus, the ordinarily skilled artisan would realize that if an attempt is made to enrich and expand the cells of Inaba, the cells of Inaba can no longer uptake antigen, and so cannot be antigen-activated, as is required by the present claims.
>
> Accordingly, the cells of Inaba are simply not the same as those of the claimed invention.

(emphasis in original)

Ultimately, the rejection over Inaba was withdrawn (Office Action of 13 August 2004, page 2, #2), which stated:

> In view of Applicant's remarks/arguments the previous rejections under 35 U.S.C. 103(a)...have been withdrawn. **In particular, Applicant's arguments that the cells of the instant invention are not the cells of the reference because the cells of the reference were not cultured in GM-CSF, has been found convincing.**

As noted above, culture in GM-CSF is essential to the development of *in vitro* cultures of proliferating precursor cells of the present claims. Neither the Inaba reference cited earlier nor the Pancholi reference cited in the outstanding Office Action nor the Steinman reference cited in the outstanding Office Action taught this critical feature of the invention. Accordingly, the claimed invention cannot be anticipated by or rendered obvious by any of these references and Applicants respectfully request that these rejections of the claims be withdrawn.

The Invention

"The present invention provides **for the first time a method of obtaining dendritic cells in sufficient quantities to be used to treat or immunize animals or humans with dendritic cells which have been activated with antigens**" (specification at page 40, lines 25-28 and page 9, line 35 through page 10, line 4). Specifically, the invention provides "a method of producing cultures of proliferating dendritic cell precursors which mature *in vitro* to mature dendritic cells. The dendritic cells and the dendritic cell precursors produced according to the method of the invention may be produced in amounts suitable for various immunological interventions for the prevention and treatment of disease" (see the specification at page 19, lines 25-31 (the first paragraph of the Detailed Description of the Invention)). In this manner, the invention overcomes the previously existing problem in the art of not being able to obtain sufficient quantities of dendritic cells in culture for clinical treatment (as discussed, for example, in the Background section on page 2, second paragraph, and on page 8, lines 8-10).

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the rejections of claims have been overcome and that the claims are in condition for allowance. However, if the

Examiner believes that any further discussion of this communication would be helpful, he is encouraged to contact the undersigned by telephone.

Applicants respectfully request a Three Month Extension of Time for the filing of this response. Please apply the charge of $1,050.00 to Deposit Account No. 50-3187.

No additional fees or extensions of time are believed to be due in connection with this communication except for those indicated in documents accompanying this paper. However, if any additional extensions of time are necessary for the consideration of this paper, such extensions are petitioned under 37 CFR § 1.136(a). Please apply any charges that may be due for extensions of time or for net addition of claims to our Deposit Account No. 50-3187.

Respectfully submitted,

Leigh W. Thorne, Ph.D.
Attorney for Applicants
Registration No. 47,992

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As noted above, culture in GM-CSF is essential to the development of *in vitro* cultures of proliferating precursor cells of the present claims. Neither the Inaba reference cited earlier nor the Pancholi reference cited in the outstanding Office Action nor the Steinman reference cited in the outstanding Office Action taught this critical feature of the invention. Accordingly, the claimed invention cannot be anticipated by or rendered obvious by any of these references and Applicants respectfully request that these rejections of the claims be withdrawn.

The Invention

"The present invention provides **for the first time a method of obtaining dendritic cells in sufficient quantities to be used to treat or immunize animals or humans with dendritic cells which have been activated with antigens**" (specification at page 40, lines 25-28 and page 9, line 35 through page 10, line 4). Specifically, the invention provides "a method of producing cultures of proliferating dendritic cell precursors which mature *in vitro* to mature dendritic cells. The dendritic cells and the dendritic cell precursors produced according to the method of the invention may be produced in amounts suitable for various immunological interventions for the prevention and treatment of disease" (see the specification at page 19, lines 25-31 (the first paragraph of the Detailed Description of the Invention)). In this manner, the invention overcomes the previously existing problem in the art of not being able to obtain sufficient quantities of dendritic cells in culture for clinical treatment (as discussed, for example, in the Background section on page 2, second paragraph, and on page 8, lines 8-10).

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